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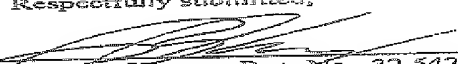
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Date: April 22, 2011	From: Brion P. Heaney MELLEN, WHITE, ZELANO & BRANIGAN, P.C. Arlington Courthouse Plaza I 2200 Clarendon Blvd., Suite 1400 Arlington, VA 22201 (U.S.A.) (Fax: 703-243-6410)
To: United States Patent and Trademark Office	Writer's Direct Dial: (703) 812-5315
Attn: Office of Patent Legal Administration	Writer's Internet Address: eopp@mwzab.com
Facsimile No.: 571-273-0100	Re: Patent Term Extension Application for: U.S. Patent: 6,441,168
Telephone No.:	Filed: November 23, 2010
	Our Ref: BAYSCH-0290-X (EPROV-0015)
Total No. of Pages: 46; if you do not receive all pages, please call (703) 243-6333	

Dear Assistant Commissioner for Patents:  
The documents which follow related to the above matter are:

- Response to Order to Show Cause (3 pages)
- Declaration Under 37 C.F.R. 1.132 (2 pages)
- Exhibit A - NDA Approval (39 pages)
- Exhibit B - Email from FDA dated September 24, 2010 (1 page)

Respectfully submitted,

  
Brion P. Heaney, Reg. No. 32,542  
Attorney for Applicant

## CERTIFICATION OF FACSIMILE TRANSMISSION

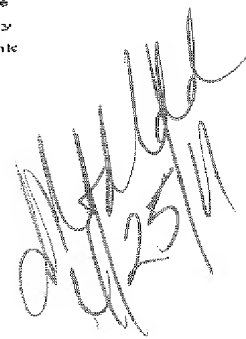
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## F A C S I M I L E

Date: April 22, 2011

To: United States Patent and Trademark Office

Attn: Office of Patent Legal Administration

Facsimile No.: 571-273-0100

Telephone No.:

From: Brion P. Heaney

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.

Arlington Courthouse Plaza I

2200 Clarendon Blvd., Suite 1400

Arlington, VA 22201 (U.S.A.)

(Fax: 703-243-6410)

Writer's Direct Dial: (703) 812-5315

Writer's Internet Address: [sopp@mwzb.com](mailto:sopp@mwzb.com)

Re: Patent Term Extension Application for: U.S. Patent: 6,441,168

Filed: November 23, 2010

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Brion P. Heaney, Reg. No. 32,542  
Attorney for Applicant

### CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

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Diane Trayne

Date:

April 22, 2011

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No. 6,441,168:

Issued: August 27, 2002

Inventors: Rudolf Muller,  
Rudolf Moser, and  
Thomas Egger.

Assignee: Eprova AG

Title: Stable crystalline salts of 5-methyltetrahydrofolic acid

Assistant Commissioner for Patents  
**Mail Stop: Hatch-Waxman PTE**  
P.O Box 1450  
Alexandria, VA 22314

**RESPONSE TO ORDER TO SHOW CAUSE**

SIR:

On March 22, 2011, the USPTO issued an Order To Show Cause with regards to the Patent Term Extension Application filed November 23, 2010 for the product Beyaz<sup>TM</sup>. In the Order to Show Cause, the USPTO indicated that the application as filed did not demonstrate that the application had been filed "within" the sixty day period set forth in 35 USC §156(d)(1). The USPTO argued that the first day of the sixty day period begins on the day permission is granted for commercial marketing or use of the product, i.e., the day of FDA Approval, citing *Unimed, Inc. v. Quigg*, 888 F.2d 826,828 (Fed. Cir. 1989).

The Order to Show Cause stated that the applicant had received FDA Approval on September 24, 2010, and therefore the PTE application was due on or before November 22, 2010. However, applicant filed the PTE application one day latter, i.e., on November 23, 2010.

The Order to Show Cause also cited *The Medicines Company v. Kappos*, 731 F. Supp.2d 470 (E.D. Va. 2010). In *The Medicines Company v. Kappos*, the court determined that the language in 35 USC §156(d)(1) should be given a business day interpretation to ensure that applicants do not lose a portion of the period Congress granted them to file the PTE application. In that case, the court further held that since Medicines Company received notice

of their NDA Approval from FDA after the close of FDA's business, i.e., after 4:30 PM EST, then the time period set forth in 35 USC §156(d)(1) would start on the next business day.

The Order to Show Cause states that there is no evidence of record indicating that Applicant received NDA Approval after 4:30 PM EST on September 24, 2010. Therefore, the USPTO assumes that the NDA Approval was transmitted to applicant during FDA's normal business hours, i.e., at or before 4:30 PM EST on September 24, 2010.

However, the facts are the same as described in *The Medicines Company v. Kappos*. Applicant received notice of their NDA Approval from FDA after the close of FDA's business, i.e., after 4:30 PM EST, on September 24, 2010. Thus, the time period set forth in 35 USC §156(d)(1) started on the next business day, i.e., September 25, 2010. Thus, the sixty day period set forth in 35 USC §156(d)(1) ended on November 23, 2010, the date that applicant filed the instant PTE application. Therefore, the application was filed "within" the sixty day period set forth in 35 USC §156(d)(1).

To demonstrate the time applicant received notice of their NDA Approval from FDA, attached herewith is a Rule 132 Declaration executed by Ms. Kavita Johal. Ms. Johal is an employee of Bayer Healthcare Pharmaceuticals, Inc. in Montville, NJ, and during the time period from August 21, 2009 to the present, she was responsible for communication with the Food and Drug Administration on behalf of Bayer Healthcare Pharmaceuticals, Inc. for the New Drug Application (NDA 022532). In the Rule 132 Declaration, Ms. Johal states that the September 24, 2010 FDA approval letter for Beyaz<sup>TM</sup> was received by Bayer Healthcare Pharmaceuticals after 4:30 PM on September 24, 2010.

In support of this statement, attached to the Declaration as Exhibit B is a copy of the September 24, 2010 email sent to Ms. Johal from Pamela Lucarelli (Regulatory Health Project Manager FDA/Center for Drug Evaluation and Research) which enclosed the NDA approval letter. A copy of the NDA approval letter is attached to the Declaration as Exhibit A.

In light of the above remarks, and the attached Declaration and Exhibits, it is respectfully submitted that applicant's PTE application for US 6,441,168 satisfies the eligibility requirement under 35 USC §156(d)(1).

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,  
/Brion P. Heaney/

---

Brion P. Heaney, Reg. No. 32,542  
Attorney for Applicant

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.  
Arlington Courthouse Plaza 1  
2200 Clarendon Boulevard, Suite 1400  
Arlington, VA 22201  
Direct Dial: 703-812-5311  
Facsimile: 703-243-6410

**Attorney Docket No.: BAYSCH-290-X**  
Date: April 22, 2011

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No. 6,441,168:

Issued: August 27, 2002

Inventors: Rudolf Muller,  
Rudolf Moser, and  
Thomas Egger.

Assignee: Eprova AG

Title: Stable crystalline salts of 5-methyltetrahydrofolic acid

Mail Stop: Hatch-Waxman PTE  
Office of Patent Legal Administration  
Room MDW 7D55  
600 Dulany Street (Madison Building)  
Alexandria, VA 22314

DECLARATION UNDER 37 C.F.R. 1.132

Mail Stop: Hatch-Waxman PTE  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450  
SIR:

I, Kavita Johal, being duly warned declare that:

I am a citizen of the United States, residing in Parsippany, New Jersey.

I am presently employed by Bayer Healthcare Pharmaceuticals, Inc. in Montville, NJ,  
in the department of Global Regulatory Affairs, Women's HealthCare.

During the time period from August 21, 2009 to the present I have been responsible  
for communication with the Food and Drug Administration on behalf of Bayer Healthcare  
Pharmaceuticals, Inc. for the New Drug Application (NDA 022532) for the approval of the  
product Beyaz<sup>TM</sup> (drospirenone/ethinyl estradiol/levomefolate calcium and levomefolate  
calcium) tablets.

Beyaz<sup>TM</sup> was approved by the FDA on September 24, 2010. Attached as Exhibit A is a copy of the NDA approval letter signed by Julie Beitz, M.D., of FDA's Office of Drug Evaluation III, Center for Drug Evaluation and Research.

This approval letter was first sent to Bayer Healthcare Pharmaceuticals, Inc. via an email dated September 24, 2010 to me from Pamela Lucarelli, a Regulatory Health Project Manager at FDA/Center for Drug Evaluation and Research, Division of Reproductive and Urologic Products. Attached as Exhibit B is a copy of the September 24, 2010 email sent to me from Pamela Lucarelli.

As indicated in Exhibit B, the email of September 24, 2010 with the attached FDA approval letter for Beyaz<sup>TM</sup> was received by Bayer Healthcare Pharmaceuticals at 4:45 PM on September 24, 2010.

I hereby declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application.



Kavita Johal

Date: 4/21/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 022532

**NDA APPROVAL**

Bayer HealthCare Pharmaceuticals Inc.  
Attention: Kavita Johal, Pharm.D.  
Assistant Director, Global Regulatory Affairs  
P.O. Box 1000  
Montville, NJ 07045

Dear Ms. Johal:

Please refer to your New Drug Application (NDA) dated August 21, 2009, received August 24, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium and levomefolate calcium) tablets.

We acknowledge receipt of your amendments dated September 25 and 30, October 7, November 17, and December 4 and 16 (2), 2009, January 11 and 21, February 3 and 4, March 1, 11 and 22, April 16, 22 and 23, May 7 and 27, July 2, 9, 14, 15 and 16, August 9 and 24, and September 23, 2010.

This new drug application provides for the use of Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium and levomefolate calcium) tablets for the following indications:

- Prevention of pregnancy;
- Treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception;
- Treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche;
- In women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is

**EXHIBIT A**



identical to the enclosed labeling text for the package insert. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on July 9, 2010, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022532.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pre-menarcheal patients because pre-menarcheal patients are not at risk of becoming pregnant and the use of this product before menarche is not indicated. We note that you have fulfilled the pediatric study requirement for post-menarcheal pediatric patients by extrapolation of adult data.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **LETTERS TO HEALTH CARE PROFESSIONALS**

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to [CDERMedWatchSafetyAlerts@fda.hhs.gov](mailto:CDERMedWatchSafetyAlerts@fda.hhs.gov), and to the following address:

MedWatch Program  
Office of Special Health Issues  
Food and Drug Administration  
10903 New Hampshire Ave  
Building 32, Mail Stop 5353  
Silver Spring, MD 20993

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Pamela Lucarelli, Regulatory Health Project Manager, at (301) 796-3961.

Sincerely,

*{See appended electronic signature page}*

Julie Beitz, M.D.

Director

Office of Drug Evaluation III

Center for Drug Evaluation and Research

Enclosure: Content of Labeling

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Beyaz safely and effectively. See full prescribing information for Beyaz.

**BEYAZ (drospirenone/ethinyl estradiol/ levomefolate calcium tablets and levomefolate calcium tablets)**

Initial U.S. Approval: 2010

### WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning

- Women over 35 years old who smoke should not use Beyaz (4).
- Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. (4)

### INDICATIONS AND USAGE

Beyaz is an estrogen/progestin COC containing a folate, indicated for use by women to:

- prevent pregnancy. (1.1)
- treat symptoms of premenstrual dysphoric disorder (PMDD) for women who choose to use an oral contraceptive for contraception. (1.2)
- treat moderate acne for women at least 14 years old only if the patient desires an oral contraceptive for birth control. (1.3)
- raise folate levels in women who choose to use an oral contraceptive for contraception. (1.4)

### DOSAGE AND ADMINISTRATION

- Take one tablet daily by mouth at the same time every day. (2.1)
- Tablets must be taken in the order directed on the blister pack. (2.1)

### DOSAGE FORMS AND STRENGTHS

Beyaz consists of 28 film-coated, biconvex tablets in the following order (3):

- 24 pink tablets, each containing 3 mg drospirenone (DRSP), 0.02 mg ethinyl estradiol (EE) as betadex clathrate and 0.451 mg levomefolate calcium
- 4 light orange tablets, each containing 0.451 mg levomefolate calcium

### CONTRAINDICATIONS

- Renal impairment or adrenal insufficiency (4)
- A high risk of arterial or venous thrombotic diseases (4)
- Undiagnosed abnormal uterine bleeding (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Liver tumors or liver disease (4)
- Pregnancy (4)

### WARNINGS AND PRECAUTIONS

- Vascular risks: Stop Beyaz if a thrombotic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Hyperkalemia: DRSP has antimineralocorticoid activity. Do not use in patients predisposed to hyperkalemia. Check serum potassium level during the first treatment cycle in women on long-term treatment with medications that may increase serum potassium. (5.2, 7.3)
- Liver disease: Discontinue Beyaz if jaundice occurs. (5.4)
- High blood pressure: Do not prescribe Beyaz for women with uncontrolled hypertension or hypertension with vascular disease. (5.5)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking Beyaz. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.7)
- Headache: Evaluate significant change in headaches and discontinue Beyaz if indicated. (5.8)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea. (5.9)

### ADVERSE REACTIONS

- The most frequent ( $\geq 2\%$ ) adverse reactions in contraception, acne and folate clinical trials were: headache/migraine (5.9%), menstrual irregularities (4.1%), nausea/vomiting (3.5%) and breast pain/tenderness (3.2%).
- The most frequent ( $> 2\%$ ) adverse reactions in PMDD clinical were: menstrual irregularities (24.9%), nausea (15.8%), headache (13.0%), breast tenderness (10.5%), fatigue (4.2%), irritability (2.8%), decreased libido (2.8%), increased weight (2.5%), and affect lability (2.1%).

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

### DRUG INTERACTIONS

- Drugs or herbal products that induce certain enzymes (e.g., CYP3A4) may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

### USE IN SPECIFIC POPULATIONS

- Nursing mothers: Not recommended; can decrease milk production. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling

Revised: 9/2010

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

- 1.1 Oral Contraceptive
- 1.2 Premenstrual Dysphoric Disorder (PMDD)
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- 2.2 How to Start Beyaz
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- 16.1 How Supplied
- 16.2 Storage Conditions

17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed

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## FULL PRESCRIBING INFORMATION

### **WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS**

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke. *[See Contraindications (4)].*

## **1 INDICATIONS AND USAGE**

### **1.1 Oral Contraceptive**

Beyaz is indicated for use by women to prevent pregnancy.

### **1.2 Premenstrual Dysphoric Disorder (PMDD)**

Beyaz is also indicated for the treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception. The effectiveness of Beyaz for PMDD when used for more than three menstrual cycles has not been evaluated.

The essential features of PMDD according to the Diagnostic and Statistical Manual-4th edition (DSM-IV) include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating and weight gain. In this disorder, these symptoms occur regularly during the luteal phase and remit within a few days following onset of menses; the disturbance markedly interferes with work or school, or with usual social activities and relationships with others. Diagnosis is made by healthcare providers according to DSM-IV criteria, with symptomatology assessed prospectively over at least two menstrual cycles. In making the diagnosis, care should be taken to rule out other cyclical mood disorders.

Beyaz has not been evaluated for the treatment of premenstrual syndrome (PMS).

### **1.3 Acne**

Beyaz is indicated for the treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche. Beyaz should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control.

### **1.4 Folate Supplementation**

Beyaz is indicated in women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product.

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 How to Take Beyaz**

Take one tablet by mouth at the same time every day. The failure rate may increase when pills are missed or taken incorrectly.

To achieve maximum contraceptive and PMDD effectiveness, Beyaz must be taken as directed. Single missed pills should be taken as soon as remembered.

### **2.2 How to Start Beyaz**

Instruct the patient to begin taking Beyaz either on the first day of her menstrual period (Day 1 Start) or on the first Sunday after the onset of her menstrual period (Sunday Start).

### *Day 1 Start*

During the first cycle of Beyaz use, instruct the patient to take one pink Beyaz daily, beginning on Day one (1) of her menstrual cycle. (The first day of menstruation is Day one.) She should take one pink Beyaz daily for 24 consecutive days, followed by one light orange tablet daily on days 25 through 28. Beyaz should be taken in the order directed on the package at the same time each day, preferably after the evening meal or at bedtime with some liquid, as needed. Beyaz can be taken without regard to meals. If Beyaz is first taken later than the first day of the menstrual cycle, Beyaz should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

### *Sunday Start*

During the first cycle of Beyaz use, instruct the patient to take one pink Beyaz daily, beginning on the first Sunday after the onset of her menstrual period. She should take one pink Beyaz daily for 24 consecutive days, followed by one light orange tablet daily on days 25 through 28. Beyaz should be taken in the order directed on the package at the same time each day, preferably after the evening meal or at bedtime with some liquid, as needed. Beyaz can be taken without regard to meals. Beyaz should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient should begin her next and all subsequent 28-day regimens of Beyaz on the same day of the week that she began her first regimen, following the same schedule. She should begin taking her pink tablets on the next day after ingestion of the last light orange folate tablet, regardless of whether or not a menstrual period has occurred or is still in progress. Anytime a subsequent cycle of Beyaz is started later than the day following administration of the last light orange tablet, the patient should use another method of contraception until she has taken a pink Beyaz daily for seven consecutive days.

### *When switching from a different birth control pill*

When switching from another birth control pill, Beyaz should be started on the same day that a new pack of the previous oral contraceptive would have been started.

### *When switching from a method other than a birth control pill*

When switching from a transdermal patch or vaginal ring, Beyaz should be started when the next application would have been due. When switching from an injection, Beyaz should be started when the next dose would have been due. When switching from an intrauterine contraceptive or an implant, Beyaz should be started on the day of removal.

Withdrawal bleeding usually occurs within 3 days following the last pink tablet. If spotting or breakthrough bleeding occurs while taking Beyaz, instruct the patient to continue taking her Beyaz by the regimen described above. Counsel her that this type of bleeding is usually transient and without significance; however, advise her that if the bleeding is persistent or prolonged, she should consult her healthcare provider.

Although the occurrence of pregnancy is low if Beyaz is taken according to directions, if withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy. Discontinue Beyaz if pregnancy is confirmed.

The risk of pregnancy increases with each active pink tablet missed. For additional patient instructions regarding missed pills, see the **"WHAT TO DO IF YOU MISS PILLS"** section in the **FDA Approved Patient Labeling** which follows. If breakthrough bleeding occurs following missed tablets, it will usually be transient and of no consequence. If the patient misses one or more light orange tablets, she should still be protected against pregnancy provided she begins taking a new cycle of pink tablets on the proper day.

For postpartum women who do not breastfeed or after a second trimester abortion, start Beyaz no earlier than 4 weeks postpartum due to the increased risk of thromboembolism. If the patient starts on Beyaz postpartum and has not yet had a period, evaluate for possible pregnancy, and instruct her to use an additional method of contraception until she has taken Beyaz for 7 consecutive days.

### 2.3 Advice in Case of Gastrointestinal Disturbances

In case of severe vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after tablet-taking, this can be regarded as a missed tablet.

### 2.4 Folate Supplementation

The U.S. Preventive Services Task Force recommends that women of childbearing age consume supplemental folic acid in a dose of at least 0.4 mg (400 mcg) daily.<sup>1</sup> Consider other folate supplementation that a woman may be taking before prescribing Beyaz. Ensure that folate supplementation is maintained if a woman discontinues Beyaz due to pregnancy.

## 3 DOSAGE FORMS AND STRENGTHS

Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) is available in blister packs.

Each blister pack (28 film-coated tablets) contains in the following order:

- 24 pink tablets each containing 3 mg drospirenone (DRSP), 0.02 mg ethinyl estradiol (EE) as betadex clathrate and 0.451 mg levomefolate calcium
- 4 light orange tablets each containing 0.451 mg levomefolate calcium

## 4 CONTRAINDICATIONS

Do not prescribe Beyaz to women who are known to have the following:

- Renal impairment
- Adrenal insufficiency
- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 [*see Boxed Warning and Warnings and Precautions (5.1)*]
  - Have deep vein thrombosis or pulmonary embolism, now or in the past [*see Warnings and Precautions (5.1)*]
  - Have cerebrovascular disease [*see Warnings and Precautions (5.1)*]
  - Have coronary artery disease [*see Warnings and Precautions (5.1)*]
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [*see Warnings and Precautions (5.1)*]
  - Have inherited or acquired hypercoagulopathies [*see Warnings and Precautions (5.1)*]
  - Have uncontrolled hypertension [*see Warnings and Precautions (5.5)*]
  - Have diabetes mellitus with vascular disease [*see Warnings and Precautions (5.7)*]
  - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 [*see Warnings and Precautions (5.8)*]
- Undiagnosed abnormal uterine bleeding [*see Warnings and Precautions (5.9)*]
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past [*see Warnings and Precautions (5.3)*]
- Liver tumors, benign or malignant, or liver disease [*see Warnings and Precautions (5.4)* and *Use in Specific Populations (8.7)*]
- Pregnancy, because there is no reason to use COCs during pregnancy [*see Warnings and Precautions (5.10)* and *Use in Specific Populations (8.1)*]

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Thromboembolic Disorders and Other Vascular Problems

Stop Beyaz if an arterial or deep venous thrombotic (VTE) event occurs. Although the use of COCs increases the risk of venous thromboembolism, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of venous thromboembolism in women using COCs is 3 to 9 per 10,000 woman-years. The risk is highest during the first year of use of a COC. Use of COCs also increases the risk of arterial thromboses such as strokes and



myocardial infarctions, especially in women with other risk factors for these events. The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

If feasible, stop Beyaz at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start Beyaz no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with other underlying risk factors.

Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Stop Beyaz if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately. [See *Adverse Reactions* (6).]

#### *Epidemiologic studies including a DRSP-containing COC*

Several studies have investigated the relative risks of thromboembolism in women using a different DRSP-containing COC (Yasmin, which contains 0.03 mg of EE and 3 mg of DRSP) compared to those in women using COCs containing other progestins. Two prospective cohort studies, both evaluating the risk of venous and arterial thromboembolism and death, were initiated at the time of Yasmin approval.<sup>2,3</sup> The first (EURAS) showed the risk of thromboembolism (particularly venous thromboembolism) and death in Yasmin users to be comparable to that of other oral contraceptive preparations, including those containing levonorgestrel (a so-called second generation COC). The second prospective cohort study (Ingenix) also showed a comparable risk of thromboembolism in Yasmin users compared to users of other COCs, including those containing levonorgestrel. In the second study, COC comparator groups were selected based on their having similar characteristics to those being prescribed Yasmin.

Two additional epidemiological studies, one case-control study (van Hylekama Vlieg et al.<sup>4</sup>) and one retrospective cohort study (Lidegaard et al.<sup>5</sup>) suggested that the risk of venous thromboembolism occurring in Yasmin users was higher than that for users of levonorgestrel-containing COCs and lower than that for users of desogestrel/gestodene-containing COCs (so-called third generation COCs). In the case-control study, however, the number of Yasmin cases was very small (1.2% of all cases) making the risk estimates unreliable. The relative risk for Yasmin users in the retrospective cohort study was greater than that for users of other COC products when considering women who used the products for less than one year. However, these one-year estimates may not be reliable because the analysis may include women of varying risk levels. Among women who used the product for 1 to 4 years, the relative risk was similar for users of Yasmin to that for users of other COC products.

### **5.2 Hyperkalemia**

Beyaz contains 3 mg of the progestin DRSP which has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. Beyaz should not be used in patients with conditions that predispose to hyperkalemia (i.e., renal insufficiency, hepatic dysfunction and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium should have their serum potassium level checked during the first treatment cycle. Medications that may increase serum potassium include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and NSAIDs.

### **5.3 Carcinoma of the Breasts and Reproductive Organs**

Women who currently have or have had breast cancer should not use Beyaz because breast cancer is a hormonally-sensitive tumor.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

## **5.4 Liver Disease**

Discontinue Beyaz if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded.

Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

Oral contraceptive-related cholestasis may occur in women with a history of pregnancy-related cholestasis. Women with a history of COC-related cholestasis may have the condition recur with subsequent COC use.

## **5.5 High Blood Pressure**

For women with well-controlled hypertension, monitor blood pressure and stop Beyaz if blood pressure rises significantly. Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use. The incidence of hypertension increases with increasing concentration of progestin.

## **5.6 Gallbladder Disease**

Studies suggest a small increased relative risk of developing gallbladder disease among COC users.

## **5.7 Carbohydrate and Lipid Metabolic Effects**

Carefully monitor prediabetic and diabetic women who are taking Beyaz. COCs may decrease glucose tolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

## **5.8 Headache**

If a woman taking Beyaz develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Beyaz if indicated.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

## **5.9 Bleeding Irregularities**

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

Data for Beyaz show the average number of episodes of bleeding per reference period (90 days) was 3.2 in Cycles 4-6. The average number of bleeding and/or spotting days with Beyaz was 15.1 days. The intensity of bleeding for Beyaz based on the ratio of spotting-only days versus total bleeding and/or spotting days was 5.2/15.1 days.

Based on patient diaries from two contraceptive clinical trials of YAZ, 8 to 25% of women experienced unscheduled bleeding per 28-day cycle. A total of 12 subjects out of 1,056 (1.1%) discontinued YAZ due to menstrual disorders including intermenstrual bleeding, menorrhagia, and metrorrhagia.

Women who use Beyaz may experience absence of withdrawal bleeding, even if they are not pregnant. Based on subject diaries from YAZ contraception trials for up to 13 cycles, 6 to 10% of women experienced cycles with no withdrawal bleeding. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

If withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have),

consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

#### **5.10 COC Use Before or During Early Pregnancy**

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy. Discontinue Beyaz if pregnancy is confirmed and initiate a prenatal vitamin containing folate supplementation.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy [*see Use in Specific Populations (8.1)*].

#### **5.11 Depression**

Women with a history of depression should be carefully observed and Beyaz discontinued if depression recurs to a serious degree.

#### **5.12 Interference with Laboratory Tests**

The use of COCs may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid-binding globulin increase with use of COCs. DRSP causes an increase in plasma renin activity and plasma aldosterone induced by its mild antimineralocorticoid activity.

Folates may mask vitamin B12 deficiency.

#### **5.13 Monitoring**

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

#### **5.14 Other Conditions**

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs.

### **6 ADVERSE REACTIONS**

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and smoking [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Vascular events [*see Warnings and Precautions (5.1)*]
- Liver disease [*see Warnings and Precautions (5.3)*]

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

#### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

##### *Contraception, Acne and Folate Supplementation Clinical Trials*

The data provided reflect the experience with the use of YAZ (3 mg DRSP/0.02 mg EE), in the adequate and well-controlled studies for contraception (N=1,056), for moderate acne vulgaris (N=536) and folate supplementation (N=379).

For contraception, a Phase 3, multicenter, multinational, open-label study was conducted to evaluate safety and efficacy up to one year in 1,027 women aged 17-36 who took at least one dose of YAZ. A second Phase 3 study was a single center, open-label, active-controlled study to evaluate the effect of 7 28-day cycles of YAZ on carbohydrate metabolism, lipids and hemostasis in 29 women aged 18-35. For acne, two multicenter, double-blind, randomized, placebo-controlled studies, in 536 women aged 14 – 45 with moderate acne vulgaris who took at least one dose of YAZ, evaluated the safety and efficacy during up to 6 cycles. For folate supplementation, the primary efficacy study using Beyaz was a multicenter, double-blind, randomized, active-controlled US trial in 379 healthy women aged 18- 40 who were treated with Beyaz or YAZ for up to 24 weeks.

The adverse reactions seen across the 3 indications overlapped, and are reported using the frequencies from the pooled dataset. The most common treatment-emergent adverse reactions ( $\geq 2\%$  of users) were: headache/migraine (5.9%), menstrual irregularities (including vaginal hemorrhage [primarily spotting], metrorrhagia and menorrhagia) (4.1%), nausea/vomiting (3.5%), and breast pain/tenderness (3.2%).

#### *PMDD Clinical Trials*

Safety data from trials for the indication of PMDD are reported separately due to differences in study design and setting in the OC, Acne and Folate Supplementation studies as compared to the PMDD clinical program.

Two (one parallel and one crossover designed) multicenter, double-blind, randomized, placebo-controlled trials for the secondary indication of treating the symptoms of PMDD evaluated safety and efficacy of YAZ during up to 3 cycles among 285 women aged 18 – 42, diagnosed with PMDD and who took at least one dose of YAZ.

Common treatment-emergent adverse reactions ( $\geq 2\%$  of users) were: menstrual irregularities (including vaginal hemorrhage [primarily spotting] and metrorrhagia) (24.9%), nausea (15.8%), headache (13.0%), breast tenderness (10.5%), fatigue (4.2%), irritability (2.8%), decreased libido (2.8%), increased weight (2.5%), and affect lability (2.1%).

#### **Adverse Reactions ( $>1\%$ ) Leading to Study Discontinuation:**

##### *Contraception Clinical Trials*

Of 1,056 women, 6.6% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reactions leading to discontinuation were headache/migraine (1.6%) and nausea/vomiting (1.0%).

##### *Acne Clinical Trials*

Of 536 women, 5.4% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reaction leading to discontinuation was menstrual irregularities (including menometrorrhagia, menorrhagia, metrorrhagia and vaginal hemorrhage) (2.2%) .

##### *Folate Clinical Trial*

Of 285 women, 4.6% who used Beyaz or YAZ discontinued from the clinical trials due to an adverse reaction; no reaction leading to discontinuation occurred in  $\geq 1\%$  of women.

##### *PMDD Clinical Trials*

Of 285 women, 11.6% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reactions leading to discontinuation were: nausea/vomiting (4.6%), menstrual irregularity (including vaginal hemorrhage, menorrhagia, menstrual disorder, menstruation irregular and metrorrhagia) (4.2%), fatigue (1.8%), breast tenderness (1.4%), depression (1.4%), headache (1.1%), and irritability (1.1%).

#### **Serious Adverse Reactions (Definitely, Probably, or Possibly Related to Study Drug):**

*Contraception Clinical Trials:* migraine and cervical dysplasia

*Acne Clinical Trials:* none reported in the clinical trials

*Folate Supplementation Clinical Trial:* cervix carcinoma stage 0

*PMDD Clinical Trials:* cervical dysplasia

## **6.2 Postmarketing Experience**

The following adverse reactions have been identified during post approval use of YAZ. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions are grouped into System Organ Classes, and ordered by frequency.

Vascular disorders: Venous and arterial thromboembolic events (including pulmonary emboli, deep vein thrombosis, cerebral thrombosis, retinal thrombosis, myocardial infarction and stroke), hypertension (including hypertensive crisis)

Hepatobiliary disorders: gallbladder disease, liver function disturbances, liver tumors

Immune system disorders: Hypersensitivity (including anaphylactic reaction)

Metabolism and nutrition disorders: Hyperkalemia, hypertriglyceridemia, changes in glucose tolerance or effect on peripheral insulin resistance (including diabetes mellitus)

Skin and subcutaneous tissue disorders: Chloasma, angioedema, erythema nodosum, erythema multiforme

Gastrointestinal disorders: Inflammatory bowel disease

Musculoskeletal and connective tissue disorders: Systemic lupus erythematosus

## 7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

### 7.1 Effects of Other Drugs on Combined Hormonal Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma levels of COCs: Co-administration of atorvastatin and certain COCs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

HIV Protease Inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels of estrogen and progestin have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Effect on DRSP: The main metabolites of DRSP in human plasma are generated without involvement of the cytochrome P450 system. Inhibitors of this enzyme system are therefore unlikely to influence the metabolism of DRSP.

### 7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

*In vitro* and clinical studies did not indicate an inhibitory potential of DRSP towards human CYP450 enzymes at clinically relevant concentrations [see *Clinical Pharmacology* (12.3)].

### **7.3 Interactions that Have the Potential to Increase Serum Potassium**

There is a potential for an increase in serum potassium in women taking Beyaz with other drugs that may increase serum potassium [see *Warnings and Precautions* (5.2) and *Clinical Pharmacology* (12.3)].

### **7.4 Effects of Folates on Other Drugs**

Folates may modify the pharmacokinetics or pharmacodynamics of certain antifolate drugs, e.g., antiepileptics (such as phenytoin), methotrexate or pyrimethamine, and may result in a decreased pharmacological effect of the antifolate drug.

### **7.5 Effects of Other Drugs on Folates**

Several drugs have been reported to reduce folate levels by inhibition of the dihydrofolate reductase enzyme (e.g., methotrexate and sulfasalazine) or by reducing folate absorption (e.g., cholestyramine), or via unknown mechanisms (e.g., antiepileptics such as carbamazepine, phenytoin, phenobarbital, primidone and valproic acid).

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. COCs should not be used during pregnancy to treat threatened or habitual abortion.

Women who do not breastfeed may start COCs no earlier than four weeks postpartum.

### **8.3 Nursing Mothers**

When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing OCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

After oral administration of 3 mg DRSP/0.03 mg EE tablets (Yasmin), about 0.02% of the DRSP dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 0.003 mg DRSP in an infant.

Studies to date indicate there is no adverse effect of folate on nursing infants.

### **8.4 Pediatric Use**

Safety and efficacy of Beyaz has been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

### **8.5 Geriatric Use**

Beyaz has not been studied in postmenopausal women and is not indicated in this population.

### **8.6 Patients with Renal Impairment**

Beyaz is contraindicated in patients with renal impairment [see *Contraindications* (4) and *Warnings and Precautions* (5.2)].

Following administration of DRSP 3 mg daily for 14 days, serum DRSP levels in subjects with mild renal impairment (creatinine clearance CL<sub>cr</sub>, 50-80 mL/min) were comparable to those in subjects with normal renal function (CL<sub>cr</sub>, >80 mL/min). The serum DRSP levels were on average 37 % higher in subjects with moderate renal impairment (CL<sub>cr</sub>, 30 - 50 mL/min) compared to those with normal renal function. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in five of the seven subjects who continued use of potassium sparing drugs during the study, mean serum potassium levels increased by up to 0.33

mEq/L. Therefore, potential exists for hyperkalemia to occur in subjects with renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium sparing drugs [see *Clinical Pharmacology* (12.3)].

### 8.7 Patients with Hepatic Impairment

Beyaz is contraindicated in patients with hepatic disease [see *Contraindications* (4) and *Warnings and Precautions* (5.4)]. The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. Beyaz has not been studied in women with severe hepatic impairment.

## 10 OVERDOSAGE

There have been no reports of serious ill effects from overdose, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

DRSP however, is a spironolactone analogue which has antimineralocorticoid properties. Serum concentration of potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

Levomefolate calcium doses of 17 mg/day (37-fold higher than the levomefolate calcium dose of Beyaz) were well tolerated after long-term treatment up to 12 weeks.

## 11 DESCRIPTION

Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) provides an oral contraceptive regimen consisting of 28 film-coated tablets that contain the active ingredients specified for each tablet below:

- 24 pink tablets each containing 3 mg DRSP, 0.02 mg EE as betadex clathrate, and 0.451 mg levomefolate calcium
- 4 light orange tablets each containing 0.451 mg levomefolate calcium

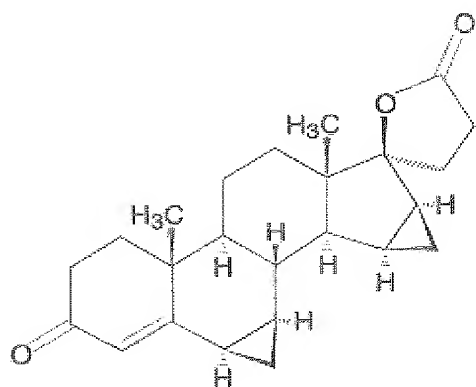
The inactive ingredients in the pink tablets are lactose monohydrate NF, microcrystalline cellulose NF, croscarmellose sodium NF, hydroxypropyl cellulose NF, magnesium stearate NF, hypromellose USP, titanium dioxide USP, talc USP, polyethylene glycol NF, ferric oxide pigment, red NF. The light orange film-coated tablets contain 0.451 mg of levomefolate calcium. The inactive ingredients in the light orange tablets are lactose monohydrate NF, microcrystalline cellulose NF, croscarmellose sodium NF, hydroxypropyl cellulose NF, magnesium stearate NF, hypromellose USP, titanium dioxide USP talc USP, polyethylene glycol NF, ferric oxide pigment, red NF, ferric oxide pigment, yellow NF.

Drospirenone (6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11, 12,13,14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17H-dicyclopropa- [6,7:15,16] cyclopenta[a]phenanthrene-17,2'(5H)-furan]-3,5'(2H)-dione) is a synthetic progestational compound and has a molecular weight of 366.5 and a molecular formula of  $C_{24}H_{30}O_3$ .

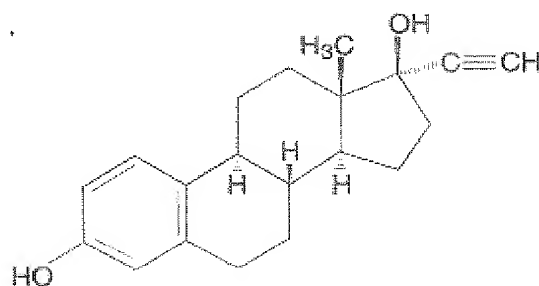
Ethinyl estradiol (19-nor-17 $\alpha$ -pregna 1,3,5(10)-triene-20-yne-3, 17-diol) is a synthetic estrogenic compound and has a molecular weight of 296.4 and a molecular formula of  $C_{20}H_{24}O_2$ .

Levomefolate calcium (N-[4-[[[2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-(6S)-pteridiny]methyl]amino]benzoyl]-L-glutamic acid, calcium salt) is a synthetic calcium salt of L-5-methyltetrahydrofolate (L-5-methyl-THF), which is a metabolite of vitamin B<sub>9</sub> and has a molecular weight of 497.5 and a molecular formula of  $C_{20}H_{23}CaN_7O_6$ .

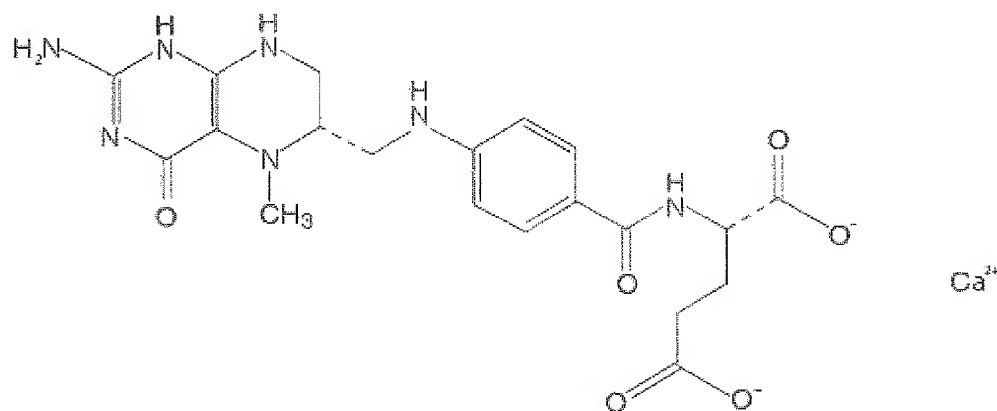
The structural formulas are as follows:



Drospirenone



Ethinyl estradiol



Levomefolate Calcium

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

### 12.2 Pharmacodynamics

Drospirenone is a spironolactone analogue with antimineralocorticoid and antiandrogenic activity. The estrogen in Beyaz is ethinyl estradiol.

#### *Contraception*

No specific pharmacodynamic studies were conducted with Beyaz.

#### *Acne*

Acne vulgaris is a skin condition with a multifactorial etiology including androgen stimulation of sebum production. While the combination of EE and DRSP increases sex hormone binding globulin (SHBG) and decreases free testosterone, the relationship between these changes and a decrease in the severity of facial acne in otherwise healthy women with this skin condition has not been established. The impact of the antiandrogenic activity of DRSP on acne is not known.



## Folate Supplementation

Two studies evaluated the impact of Beyaz on plasma folate and RBC folate levels. A randomized, double-blind, active-controlled, parallel group study compared plasma folate and red blood cell (RBC) folate levels during a 24-week treatment with YAZ + 0.451 mg levomefolate calcium as compared to YAZ alone in a U.S. population. The pharmacodynamic effect on plasma folate, RBC folate, and the profile of circulating folate metabolites was assessed during 24 weeks of treatment with 0.451 mg levomefolate calcium or with 0.4 mg folic acid (equimolar dose to 0.451 mg levomefolate calcium), both in combination with 3 mg DRSP/0.03 mg EE (Yasmin) followed by 20 weeks of open-label treatment with Yasmin only (elimination phase). [See *Clinical Studies*, 14.4]

### 12.3 Pharmacokinetics

#### Absorption

Beyaz and YAZ are bioequivalent with respect to DRSP and EE.

The absolute bioavailability of DRSP from a single entity tablet is about 76%. The absolute bioavailability of EE is approximately 40% as a result of presystemic conjugation and first-pass metabolism. The absolute bioavailability of Beyaz, which is a combination tablet of DRSP and EE stabilized by betadex as a clathrate (molecular inclusion complex), has not been evaluated. The bioavailability of EE is similar when dosed via a betadex clathrate formulation compared to when it is dosed as a free steroid. Serum concentrations of DRSP and EE reached peak levels within 1-2 hours after administration of Beyaz.

The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1-10 mg. Following daily dosing of YAZ, steady state DRSP concentrations were observed after 8 days. There was about 2 to 3 fold accumulation in serum C<sub>max</sub> and AUC (0-24h) values of DRSP following multiple dose administration of YAZ (see Table I).

For EE, steady-state conditions are reported during the second half of a treatment cycle. Following daily administration of YAZ serum C<sub>max</sub> and AUC (0-24h) values of EE accumulate by a factor of about 1.5 to 2 (see Table I).

Levomefolate calcium is structurally identical to L-5-methyltetrahydrofolate (L-5-methyl-THF), a metabolite of vitamin B<sub>9</sub>. Mean baseline concentrations of about 15 nmol/L are reached in populations without folate food fortification under normal nutritional conditions. Orally administered levomefolate calcium is absorbed and incorporated into the body folate pool. Peak plasma concentrations of about 50 nmol/L above baseline are reached within 0.5 – 1.5 hours after single oral administration of 0.451 mg levomefolate calcium.

Steady state conditions for total folate in plasma after intake of 0.451 mg levomefolate calcium are reached after about 8-16 weeks depending on the baseline levels. In red blood cells achievement of steady state is delayed due to the long life-span of red blood cells of about 120 days.

TABLE I: TABLE OF PHARMACOKINETIC PARAMETERS OF YAZ (DRSP 3 mg and EE 0.02 mg)

DRSP					
Cycle / Day	No. of Subjects	C <sub>max</sub> <sup>a</sup> (ng/mL)	T <sub>max</sub> <sup>b</sup> (h)	AUC(0-24h) <sup>a</sup> (ng•h/mL)	t <sub>1/2</sub> <sup>a</sup> (h)
1/1	23	38.4 (25)	1.5 (1-2)	268 (19)	NA <sup>c</sup>
1/21	23	70.3 (15)	1.5 (1-2)	763 (17)	30.8 (22)
EE					
Cycle / Day	No. of Subjects	C <sub>max</sub> <sup>a</sup> (pg/mL)	T <sub>max</sub> <sup>b</sup> (h)	AUC(0-24h) <sup>a</sup> (pg•h/mL)	t <sub>1/2</sub> <sup>a</sup> (h)
1/1	23	32.8 (45)	1.5 (1-2)	108 (52)	NA <sup>c</sup>
1/21	23	45.1 (35)	1.5 (1-2)	220 (57)	NA <sup>c</sup>

a) geometric mean (geometric coefficient of variation)

b) median (range)

c) NA = Not available

### *Food Effect*

The rate of absorption of DRSP and EE following single administration of a formulation similar to Beyaz was slower under fed (high fat meal) conditions with the serum  $C_{max}$  being reduced about 40% for both components. The extent of absorption of DRSP, however, remained unchanged. In contrast, the extent of absorption of EE was reduced by about 20% under fed conditions.

The effect of food on absorption of levomefolate calcium following administration of Beyaz has not been evaluated.

### *Distribution*

DRSP and EE serum levels decline in two phases. The apparent volume of distribution of DRSP is approximately 4 L/kg and that of EE is reported to be approximately 4–5 L/kg.

DRSP does not bind to sex hormone binding globulin (SHBG) or corticosteroid binding globulin (CBG) but binds about 97% to other serum proteins. Multiple dosing over 3 cycles resulted in no change in the free fraction (as measured at trough levels). EE is reported to be highly but non-specifically bound to serum albumin (approximately 98.5 %) and induces an increase in the serum concentrations of both SHBG and CBG. EE induced effects on SHBG and CBG were not affected by variation of the DRSP dosage in the range of 2 to 3 mg.

Biphasic kinetics is reported for folates with a fast- and a slow-turnover pool. The fast turnover pool probably reflecting newly absorbed folate is consistent with the terminal half-life of approximately 4 – 5 hours after single oral administration of 0.451 mg levomefolate calcium. The slow-turnover pool reflecting turnover of folate polyglutamate has a mean residence time of greater than or equal to 100 days.

### *Metabolism*

The two main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydrodrospirenone-3-sulfate. These metabolites were shown not to be pharmacologically active. In *in vitro* studies with human liver microsomes, DRSP was metabolized only to a minor extent mainly by Cytochrome P450 3A4 (CYP3A4).

EE has been reported to be subject to presystemic conjugation in both small bowel mucosa and the liver. Metabolism occurs primarily by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronide and sulfate. CYP3A4 in the liver is responsible for the 2-hydroxylation which is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion.

L-5-methyl-THF is the predominant folate transport form in blood under physiological conditions and during folic acid and levomefolate calcium administration.

### *Excretion*

DRSP serum levels are characterized by a terminal disposition phase half-life of approximately 30 hours after both single and multiple dose regimens. Excretion of DRSP was nearly complete after ten days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38-47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17-20% of the metabolites were excreted as glucuronides and sulfates.

For EE the terminal disposition phase half-life has been reported to be approximately 24 hours. EE is not excreted unchanged. EE is excreted in the urine and feces as glucuronide and sulfate conjugates and undergoes enterohepatic circulation.

L-5-methyl-THF is eliminated from the body by urinary excretion of intact folates and catabolic products as well as fecal excretion through a biphasic kinetics process.

### *Specific Populations*

**Pediatric Use:** Safety and efficacy of Beyaz has been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated. [See Use in Specific Populations (8.4)]

**Geriatric Use:** Beyaz has not been studied in postmenopausal women and is not indicated in this population. [See Use in Specific Populations (8.5)]

**Race:** No clinically significant difference was observed between the pharmacokinetics of DRSP or EE in Japanese versus Caucasian women (age 25-35) when 3mg DRSP/20 µg EE was administered daily for 21 days. Other ethnic groups have not been specifically studied.

**Renal Impairment:** Beyaz is contraindicated in patients with renal impairment.

The effect of renal impairment on the pharmacokinetics of DRSP (3 mg daily for 14 days) and the effect of DRSP on serum potassium levels were investigated in female subjects (n=28, age 30-65) with normal renal function and mild and moderate renal impairment. All subjects were on a low potassium diet. During the study 7 subjects continued the use of potassium sparing drugs for the treatment of the underlying illness. On the 14th day (steady-state) of DRSP treatment, the serum DRSP levels in the group with mild renal impairment (creatinine clearance CL<sub>cr</sub>, 50-80 mL/min) were comparable to those in the group with normal renal function (CL<sub>cr</sub>, >80 mL/min). The serum DRSP levels were on average 37% higher in the group with moderate renal impairment (CL<sub>cr</sub>, 30-50 mL/min) compared to those in the group with normal renal function. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in five of the seven subjects who continued use of potassium sparing drugs during the study, mean serum potassium levels increased by up to 0.33 mEq/L [see *Contraindications (4)*, *Warnings and Precautions (5.2)* and *Use in Specific Populations (8.7)*].

**Hepatic Impairment:** Beyaz is contraindicated in patients with hepatic disease.

The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. Beyaz has not been studied in women with severe hepatic impairment. [see *Contraindications (4)*, *Warnings and Precautions (5.4)* and *Use in Specific Populations (8.7)*]

#### *Drug Interactions*

##### **Effects of Other Drugs on Combined Hormonal Contraceptives:**

**Substances diminishing the efficacy of COCs:** Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. [See *Drug Interactions (7.1)*.]

**Substances increasing the plasma levels of COCs:** Co-administration of atorvastatin and certain COCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels. [See *Drug Interactions (7.1)*.]

**HIV Protease Inhibitors and non-nucleoside reverse transcriptase inhibitors:** Significant changes (increase or decrease) in the plasma levels of estrogen and progestin have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors. [See *Drug Interactions (7.1)*.]

**Antibiotics:** There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids. [See *Drug Interactions (7.1)*.]

##### **Effects of Combined Oral Contraceptives on Other Drugs:**

COCs containing ethinyl estradiol may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations. [See *Drug Interactions (7.2)*.]

Metabolism of DRSP and potential effects of DRSP on hepatic cytochrome P450 (CYP) enzymes have been investigated in *in vitro* and *in vivo* studies. In *in vitro* studies DRSP did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19 and CYP3A4 with CYP2C19 being the most sensitive enzyme. The potential effect of DRSP on CYP2C19 activity was investigated in a clinical pharmacokinetic study using omeprazole as a marker substrate. In the study with 24 postmenopausal women [including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose) and the CYP2C19 product 5-hydroxy omeprazole. Furthermore, no significant effect of DRSP on the systemic clearance of the CYP3A4 product omeprazole sulfone was found. These results demonstrate that DRSP did not inhibit CYP2C19 and CYP3A4 *in vivo*. [See *Drug Interactions (7.2)*.]

Two additional clinical drug-drug interaction studies using simvastatin and midazolam as marker substrates for CYP3A4 were each performed in 24 healthy postmenopausal women. The results of these studies demonstrated that pharmacokinetics of the CYP3A4 substrates were not influenced by steady state DRSP concentrations achieved after administration of 3 mg DRSP/day. [See *Drug Interactions* (7.2).]

#### **Interactions With Drugs That Have the Potential to Increase Serum Potassium:**

There is a potential for an increase in serum potassium in women taking Beyaz with other drugs that may increase serum potassium [see *Warnings and Precautions* (5.2)].

A drug-drug interaction study of DRSP 3 mg/estradiol (E2) 1 mg versus placebo was performed in 24 mildly hypertensive postmenopausal women taking enalapril maleate 10 mg twice daily. Potassium levels were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium levels in the DRSP/E2 treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple time points over 24 hours at baseline and on Day 14. On Day 14, the ratios for serum potassium C<sub>max</sub> and AUC in the DRSP/E2 group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and 1.010 (90% CI: 0.944, 1.08), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations >5.5 mEq/L).

#### **Effects of Folates on Other Drugs:**

There is a potential that folates such as folic acid and levomefolate calcium may modify the pharmacokinetics or pharmacodynamics of certain antifolate drugs (e.g., antiepileptics, methotrexate) [See *Drug Interactions* (7.4).]

#### **Effects of other Drugs on Folate:**

Several drugs (e.g., methotrexate, sulfasalazine, cholestyramine, antiepileptics) have been reported to reduce folate levels [See *Drug Interactions* (7.5).]

### **13 NONCLINICAL TOXICOLOGY**

#### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day DRSP alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of DRSP and EE, 0.1 to 2 times the exposure (AUC of DRSP) of women taking a contraceptive dose, there was an increase in carcinomas of the harderian gland in the group that received the high dose of DRSP alone. In a similar study in rats given 10 mg/kg/day DRSP alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day DRSP and EE, 0.8 to 10 times the exposure of women taking a contraceptive dose, there was an increased incidence of benign and malignant adrenal gland pheochromocytomas in the group receiving the high dose of DRSP. Mutagenesis studies for DRSP were conducted in vivo and in vitro and no evidence of mutagenic activity was observed.

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of levomefolate. Mutagenesis studies for levomefolate were conducted in vitro and in vivo and no evidence of mutagenic activity was observed.

### **14 CLINICAL STUDIES**

#### **14.1 Oral Contraceptive Clinical Trial**

In the primary contraceptive efficacy study of YAZ (3 mg DRSP/0.02 mg EE) of up to 1 year duration, 1,027 subjects were enrolled and completed 11,480 28-day cycles of use. The age range was 17 to 36 years. The racial demographic was: 87.8% Caucasian, 4.6% Hispanic, 4.3% Black, 1.2% Asian, and 2.1% other. Women with a BMI greater than 35 were excluded from the trial. The pregnancy rate (Pearl Index) was 1.41 (95% CI [0.73 – 2.47]) per 100 woman-years of use based on 12 pregnancies that occurred after the onset of treatment and within 14 days after the last dose of YAZ in women 35 years of age or younger during cycles in which no other form of contraception was used.

#### **14.2 Premenstrual Dysphoric Disorder Clinical Trials**

Two multicenter, double-blind, randomized, placebo-controlled studies were conducted to evaluate the effectiveness of YAZ in treating the symptoms of PMDD. Women aged 18-42 who met DSM-IV criteria for PMDD, confirmed by prospective daily ratings of their symptoms, were enrolled. Both studies measured the treatment effect of YAZ using the Daily Record of Severity of Problems scale, a patient-rated instrument that assesses the symptoms that constitute the DSM-IV diagnostic criteria. The primary study was a parallel group design that included 384 evaluable women with PMDD who were randomly assigned to receive YAZ or placebo treatment for 3 menstrual cycles. The supportive study, a crossover design, was terminated prematurely prior to achieving recruitment goals due to enrollment difficulties. A total

of 64 women of reproductive age with PMDD were treated initially with YAZ or placebo for up to 3 cycles followed by a washout cycle and then crossed over to the alternate medication for 3 cycles.

Efficacy was assessed in both studies by the change from baseline during treatment using a scoring system based on the first 21 items of the Daily Record of Severity of Problems. Each of the 21 items was rated on a scale from 1 (not at all) to 6 (extreme); thus a maximum score of 126 was possible. In both trials, women who received YAZ had statistically significantly greater improvement in their Daily Record of Severity of Problems scores. In the primary study, the average decrease (improvement) from baseline was 37.5 points in women taking YAZ, compared to 30.0 points in women taking placebo.

#### 14.3 Acne Clinical Trials

In two multicenter, double blind, randomized, placebo-controlled studies, 889 subjects, ages 14 to 45 years, with moderate acne received YAZ or placebo for six 28 day cycles. The primary efficacy endpoints were the percent change in inflammatory lesions, non-inflammatory lesions, total lesions, and the percentage of subjects with a "clear" or "almost clear" rating on the Investigator's Static Global Assessment (ISGA) scale on day 15 of cycle 6, as presented in Table II:

**Table II: Efficacy Results for Acne Trials\***

	Study 1		Study 2	
	YAZ N=228	Placebo N=230	YAZ N=218	Placebo N=213
ISGA Success Rate	35 (15%)	10 (4%)	46 (21%)	19 (9%)
Inflammatory Lesions				
Mean Baseline Count	33	33	32	32
Mean Absolute (%) Reduction	15 (48%)	11 (32%)	16 (51%)	11 (34%)
Non-inflammatory Lesions				
Mean Baseline Count	47	47	44	44
Mean Absolute (%) Reduction	18 (39%)	10 (18%)	17 (42%)	11 (26%)
Total lesions				
Mean Baseline Count	80	80	76	76
Mean Absolute (%) Reduction	33 (42%)	21 (25%)	33 (46%)	22 (31%)

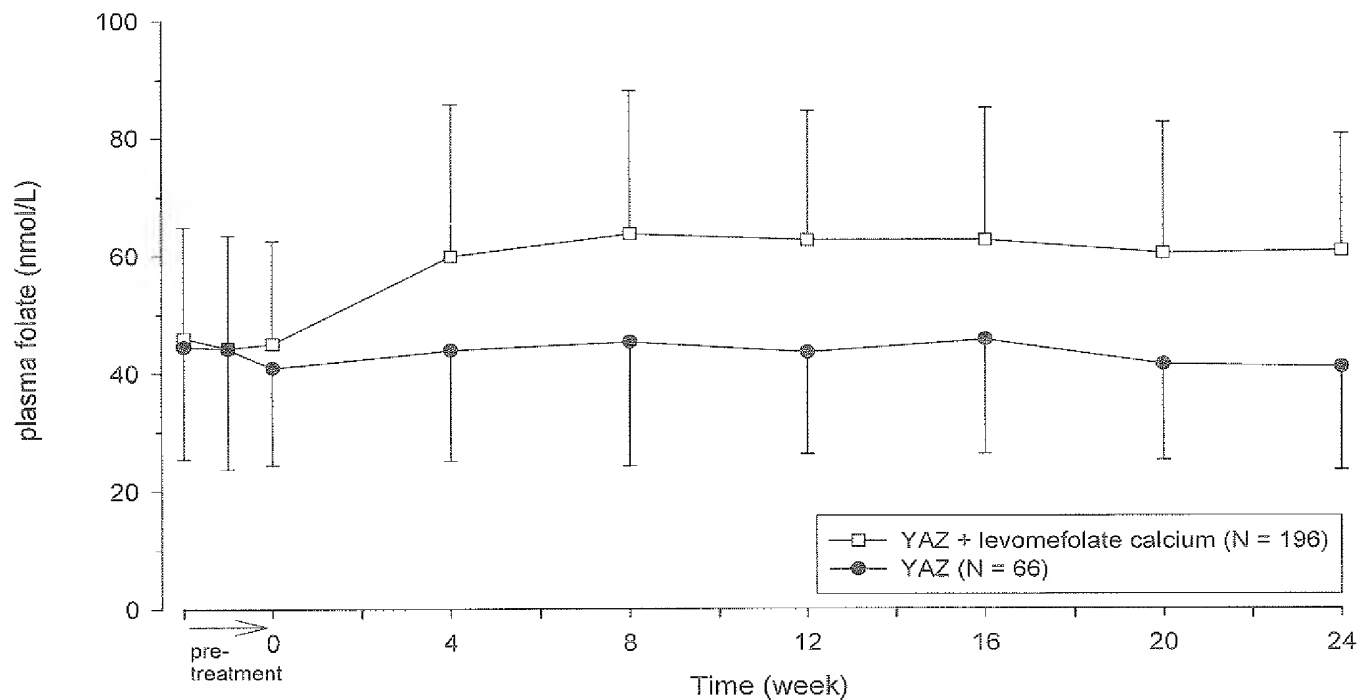
\* Evaluated at day 15 of cycle 6, last observation carried forward for the Intent to treat population

#### 14.4 Folate Supplementation Clinical Trials

The development program for Beyaz consisted of two clinical trials.

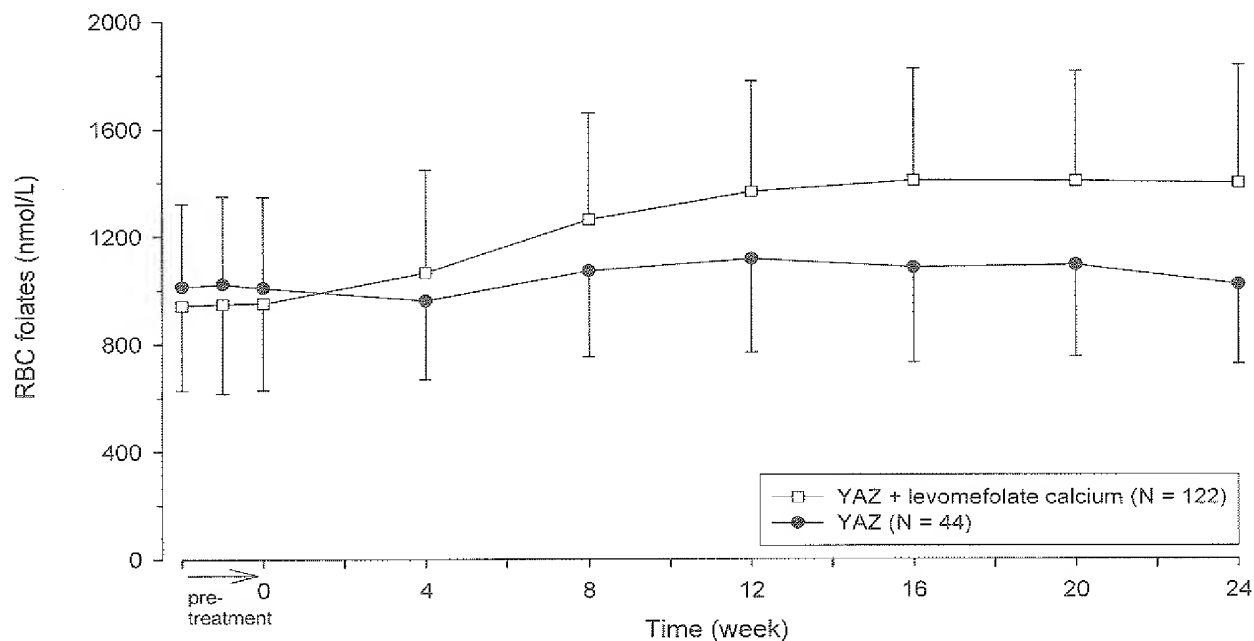
One study was a multicenter, randomized, double-blind, active-controlled, parallel group US study. Plasma folate and red blood cell folate levels were investigated during a 24-week treatment with YAZ + 0.451 mg levomefolate calcium as compared to YAZ alone in a U.S. population with folate fortified food. A total of 379 healthy women between 18 and 40 years of age with no restrictions on folate supplementation received YAZ + levomefolate calcium (N= 285) or YAZ (N=94). The plasma and RBC folate levels at Week 24 were the co-primary endpoints. Figures 1 and 2 display the results for plasma and RBC folate, respectively, among evaluable subjects in each arm of the study.

Figure 1: US Study: Mean concentration-time curves (and SD) of plasma folates after daily oral administration of YAZ + levomefolate calcium and YAZ



Arithmetic mean values based on 4-weekly measurements are displayed with arithmetic standard deviations which are shown in only one direction to improve readability. Data are based on per protocol analysis populations. The SD bar shown represents a single SD.

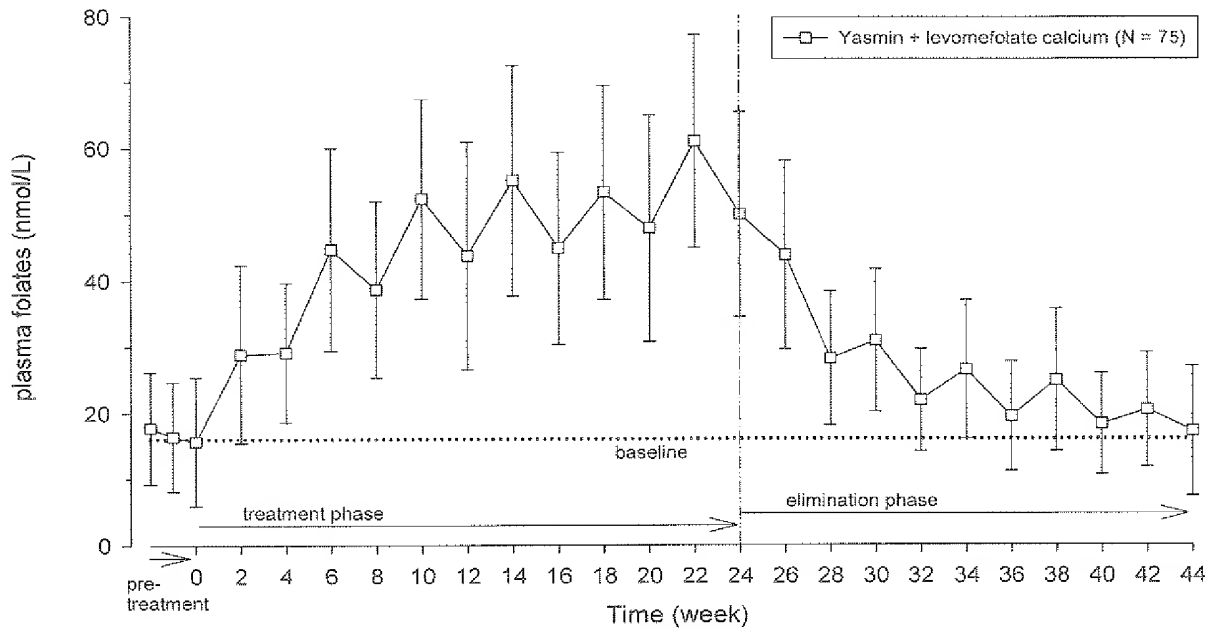
Figure 2: US Study: Mean concentration-time curves (and SD) of RBC folates after daily oral administration of YAZ + levomefolate calcium and YAZ



Arithmetic mean values based on 4-weekly measurements are displayed with arithmetic standard deviations which are shown in only one direction to improve readability. Data are based on per protocol analysis populations. The SD bar shown represents a single SD.

In the second study, the pharmacodynamic effect on plasma folate, RBC folate, and the profile of circulating folate metabolites was assessed during 24 weeks of treatment with 0.451 mg levomefolate calcium or with 0.4 mg folic acid (equimolar dose to 0.451 mg levomefolate calcium), both in combination with 3 mg DRSP/0.03 mg EE (Yasmin) followed by 20 weeks of open-label treatment with Yasmin only (elimination phase). One-hundred and seventy-two healthy women between 18 to 40 years of age from a German population without folate food fortification and without concomitant intake of folate supplements were randomized to one of the two treatments. Figures 3 and 4 display the results for plasma and RBC folate, respectively, among evaluable subjects in the levomefolate arm of the study.

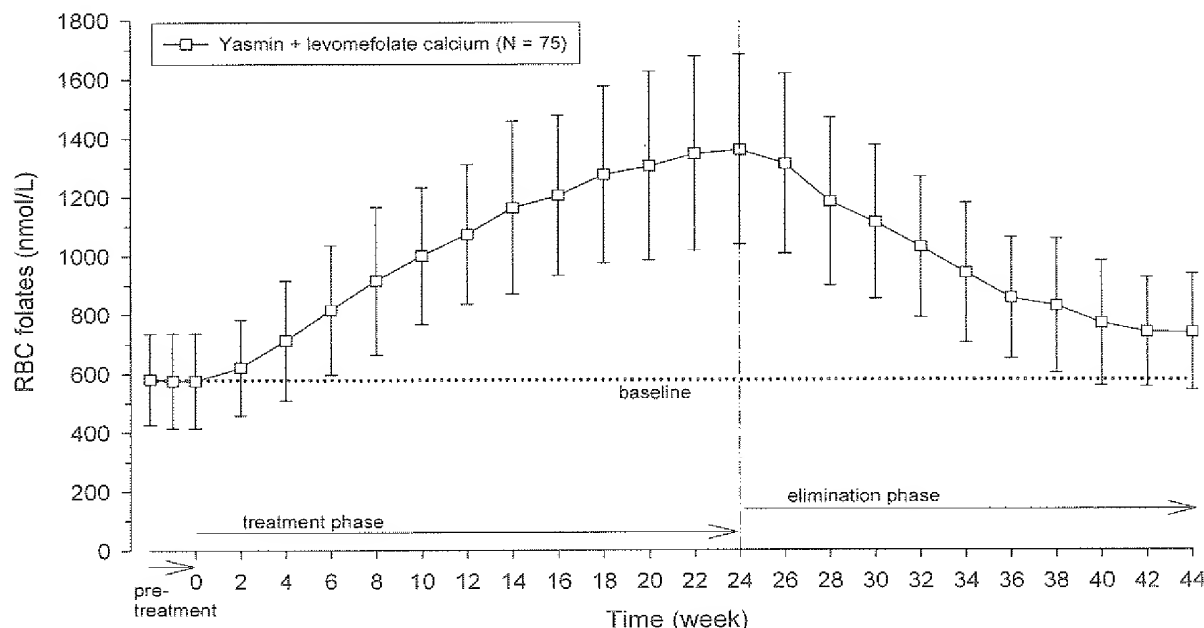
Figure 3: German Study: Mean trough concentration-time curve (and SD) of plasma folates after daily oral administration of Yasmin + levomefolate calcium



Arithmetic mean values based on biweekly measurements are displayed with arithmetic standard deviations. In the treatment phase, women received Yasmin + levomefolate calcium; in the elimination phase, all women received Yasmin only. Data are based on per protocol analysis populations. The SD bar shown represents a single SD.



Figure 4: German Study: Mean concentration-time curves (and SD) of RBC folates after daily oral administration of Yasmin + levomefolate calcium



Arithmetic mean values based on biweekly measurements are displayed with arithmetic standard deviations. In the treatment phase, women received Yasmin + levomefolate calcium; in the elimination phase, all women received Yasmin only. Data are based on per protocol analysis populations. The SD bar shown represents a single SD.

The potential to reduce the incidence of neural tube defects (NTDs) with folate supplementation is well established based on a body of evidence derived from randomized, controlled trials, nonrandomized intervention trials, and observational studies using folic acid. Therefore, the Centers for Disease Control and Prevention (CDC) and the U.S. Preventive Services Task Force recommend that women of childbearing age consume supplemental folic acid in a dose of at least 0.4 mg (400 mcg) daily <sup>1,6</sup>.

## 15 REFERENCES

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## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) are available in packages of three blister packs (NDC 50419-407-03).

The film-coated tablets are rounded with biconvex faces, one side is embossed with a regular hexagon shape with Z+ or M+.

Each blister pack (28 film-coated tablets) contains in the following order:

- 24 round, biconvex, pink, film-coated tablets with embossed “Z +” in a regular hexagon on one side each containing 3 mg drospirenone, 0.02 mg ethinyl estradiol, and 0.451 mg levomefolate calcium
- 4 round, biconvex, light orange, film-coated tablets with embossed “M+” in a regular hexagon on one side each containing 0.451 mg levomefolate calcium

### 16.2 Storage Conditions

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].

## 17 PATIENT COUNSELING INFORMATION

[See FDA-approved Patient Labeling.]

- Counsel patients that cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs.
- Counsel patients that Beyaz does not protect against HIV-infection (AIDS) and other sexually transmitted diseases.
- Counsel patients on Warnings and Precautions associated with COCs.
- Counsel patients that Beyaz contains DRSP. Drospirenone may increase potassium. Patients should be advised to inform their health care provider if they have kidney, liver or adrenal disease because the use of Beyaz in the presence of these conditions could cause serious heart and health problems. They should also inform their health care provider if they are currently on daily, long-term treatment (NSAIDs, potassium-sparing diuretics, potassium supplementation, ACE inhibitors, angiotensin-II receptor antagonists, heparin or aldosterone antagonists) for a chronic condition.
- Beyaz is not indicated during pregnancy. If pregnancy is planned or occurs during treatment with Beyaz, further intake must be stopped. However, women should be advised on the continued need of sufficient folate intake.
- Counsel patients to take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event pills are missed. *See “What to Do if You Miss Pills” section in FDA-Approved Patient Labeling.*
- Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs.
- Counsel patients who are breastfeeding or who desire to breastfeed that COCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established.
- Counsel any patient who starts COCs postpartum and who have not yet had a period, to use an additional method of contraception until she has taken a pink tablet for 7 consecutive days.
- Counsel patients that amenorrhea may occur. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles.
- Counsel patients to report whether they are taking folate supplements. Beyaz contains the equivalent of 0.4 mg (400 mcg) of folic acid.
- Counsel patients to maintain folate supplementation if they discontinue Beyaz due to pregnancy.

Manufactured for Bayer HealthCare Pharmaceuticals Inc.

Wayne, NJ 07470

Manufactured in Germany

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**WARNING TO WOMEN WHO SMOKE**

Do not use Beyaz if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects (heart and blood vessel problems) from birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

Birth control pills help to lower the chances of becoming pregnant when taken as directed. They do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

**What Is Beyaz?**

Beyaz is a birth control pill. It contains two female hormones, a synthetic estrogen called ethinyl estradiol and a progestin called drospirenone. Beyaz also contains levomefolate calcium, which is a B vitamin.

The progestin drospirenone may increase potassium. Therefore, you should not take Beyaz if you have kidney, liver or adrenal disease because this could cause serious heart and health problems. Other drugs may also increase potassium. If you are currently on daily, long-term treatment for a chronic condition with any of the medications below, you should consult your healthcare provider about whether Beyaz is right for you, and during the first month that you take Beyaz, you should have a blood test to check your potassium level.

- NSAIDs (ibuprofen [Motrin, Advil], naproxen [Aleve and others] when taken long-term and daily for treatment of arthritis or other problems)
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- ACE inhibitors (Capoten, Vasotec, Zestril and others)
- Angiotensin-II receptor antagonists (Cozaar, Diovan, Avapro and others)
- Heparin
- Aldosterone antagonists

Beyaz may also be taken to treat premenstrual dysphoric disorder (PMDD) if you choose to use the Pill for birth control. Unless you have already decided to use the Pill for birth control, you should not start Beyaz to treat your PMDD because there are other medical therapies for PMDD that do not have the same risks as the Pill. PMDD is a mood disorder related to the menstrual cycle. PMDD significantly interferes with work or school, or with usual social activities and relationships with others. Symptoms include markedly depressed mood, anxiety or tension, mood swings, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD may include breast tenderness, headache, joint and muscle pain, bloating and weight gain. These symptoms occur regularly before menstruation starts and go away within a few days following the start of the period. Diagnosis of PMDD should be made by healthcare providers.

You should only use Beyaz for treatment of PMDD if you:

- Have already decided to use oral contraceptives for birth control, and

- Have been diagnosed with PMDD by your healthcare provider.

Beyaz has not been shown to be effective for the treatment of premenstrual syndrome (PMS), a less serious set of symptoms occurring before menstruation. If you or your healthcare provider believe you have PMS, you should take Beyaz only if you want to prevent pregnancy; and not for the treatment of PMS.

Beyaz may also be taken to treat moderate acne if all of the following are true:

- Your healthcare provider says it is safe for you to use Beyaz.
- You are at least 14 years old.
- You have started having menstrual periods.
- You want to use a birth control pill to prevent pregnancy.

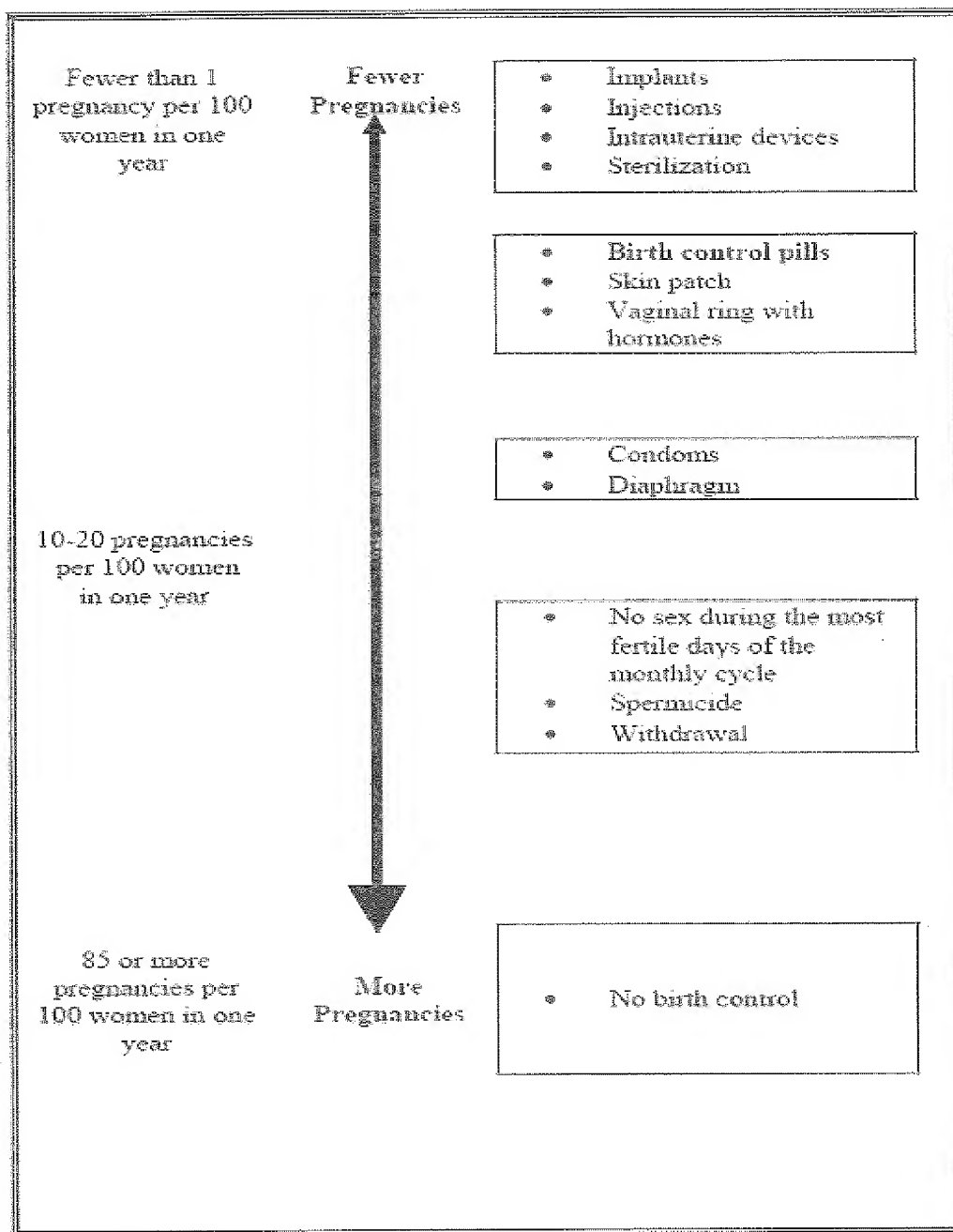
Beyaz may also be taken to provide folate supplementation in women who elect to use an oral contraceptive. It is recommended that women of reproductive age supplement their diet with 0.4 mg (400 mcg) of folic acid daily to lower their risk of having a pregnancy with a rare type of birth defect (known as a neural tube defect). The amount of folate contained in Beyaz supplements folate in the diet to lower this risk should you become pregnant while taking the drug or shortly after stopping it.

### **How Well Does Beyaz Work?**

Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of one clinical study, 1 to 2 women out of 100 women, may get pregnant during the first year they use Beyaz.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



### How Do I Take Beyaz?

1. **Be sure to read these directions** before you start taking your pills or anytime you are not sure what to do.

2. The right way to take the pill is to take one pill every day at the same time in the order directed on the package. Preferably, take the pill after the evening meal or at bedtime, with some liquid, as needed. Beyaz can be taken without regard to meals.

If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant. See "WHAT TO DO IF YOU MISS PILLS" below.

3. Many women have spotting or light bleeding at unexpected times, or may feel sick to their stomach during the first 1-3 packs of pills.

If you do have spotting or light bleeding or feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your healthcare provider.

4. Missing pills can also cause spotting or light bleeding, even when you make up these missed pills.

On the days you take two pills, to make up for missed pills, you could also feel a little sick to your stomach.

5. If you have vomiting (within 3 to 4 hours after you take your pill), you should follow the instructions for "WHAT TO DO IF YOU MISS PILLS." If you have diarrhea or if you take certain medicines, including some antibiotics and some herbal products such as St. John's Wort, your pills may not work as well.

Use a back-up method (such as condoms or spermicides) until you check with your healthcare provider.

6. If you have trouble remembering to take the pill, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.

**7. If you have any questions or are unsure about the information in this leaflet, call your healthcare provider.**

#### Before You Start Taking Your Pills

##### 1. Decide What Time of Day You Want to Take Your Pill

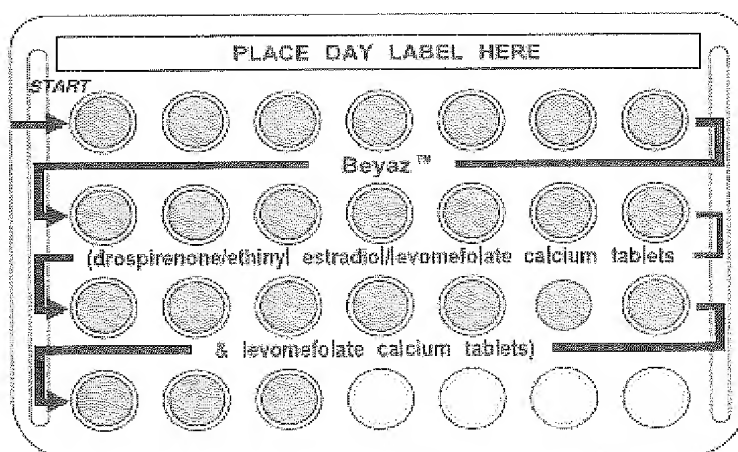
It is important to take Beyaz in the order directed on the package at the same time every day, preferably after the evening meal or at bedtime, with some liquid, as needed. Beyaz can be taken without regard to meals.

##### 2. Look at Your Pill Pack – It has 28 Pills

The Beyaz-pill pack has 24 pink pills (with hormones and folate) to be taken for 24 days, followed by 4 light orange pills (without hormones, containing folate) to be taken for the next four days. **It is important to take the light orange pills because they contain folate.**

3. Also look for:

- a) Where on the pack to start taking pills,
- b) In what order to take the pills (follow the arrows)



4. Be sure you have ready at all times (a) another kind of birth control (such as condoms or spermicides) to use as a back-up in case you miss pills, and (b) an extra, full pill pack.

### When To Start the First Pack of Pills

You have a choice for which day to start taking your first pack of pills. Decide with your healthcare provider which is the best day for you. Pick a time of day which will be easy to remember.

#### **Day 1 Start:**

1. Take the first pink pill of the pack during the first 24 hours of your period.
2. You will not need to use a back-up method of birth control, since you are starting the Pill at the beginning of your period. However, if you start Beyaz later than the first day of your period, you should use another method of birth control (such as a condom and spermicide) as a back-up method until you have taken 7 pink pills.

#### **Sunday Start:**

1. Take the first pink pill of the pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. Use another method of birth control (such as a condom and spermicide) as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). This also applies if you start Beyaz after having been pregnant, and you have not had a period since your pregnancy.

### When You Switch From a Different Birth Control Pill

When switching from another birth control pill, Beyaz should be started on the same day that a new pack of the previous birth control pill would have been started.

### When You Switch From Another Type of Birth Control Method

When switching from a transdermal patch or vaginal ring, Beyaz should be started when the next application would have been due. When switching from an injection, Beyaz should be started when the next dose would have been due. When switching from an intrauterine contraceptive or an implant, Beyaz should be started on the day of removal.

### What to Do During the Month

1. Take one pill at the same time every day until the pack is empty.

Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).

Do not skip pills even if you do not have sex very often.

2. When you finish a pack of pills, start the next pack on the day after your last light orange pill. **It is important to take the light orange pills because they contain folate.** Do not wait any days between packs.

### What to Do if You Miss Pills

#### **If you miss 1 pink pill in Week 1 of your pack:**

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take two pills in one day.
2. You do not need to use a back-up birth control method if you have sex.

#### **If you miss 2 pink pills in a row in week 1 OR week 2 of your pack:**

1. Take two pills on the day you remember and two pills the next day.
2. Then take one pill a day until you finish the pack.



3. **You could become pregnant** if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.

**If you miss 2 pink pills in a row in week 3 or week 4 of your pack:**

**1. If you are a Day 1 Starter:**

Throw out the rest of the pill pack and start a new pack that same day.

**If you are a Sunday Starter:**

Keep taking one pill every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of pills that same day.

2. **You could become pregnant** if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.

3. You may not have your period this month but this is expected. **However, if you miss your period two months in a row, call your healthcare provider because you might be pregnant.**

**If you miss 3 or more pink pills in a row during any week:**

**1. If you are a Day 1 Starter:**

Throw out the rest of the pill pack and start a new pack that same day.

**If you are a Sunday Starter:**

Keep taking 1 pill every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of pills that same day.

2. **You could become pregnant** if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as condoms or spermicides) as a back-up for those 7 days.

3. You may not have your period this month but this is expected. **However, if you miss your period two months in a row, call your healthcare provider because you might be pregnant.**

**If you miss any of the 4 light orange pills in Week 4:**

Throw away the pills you missed.

Keep taking one pill each day until the pack is empty.

You do not need a back-up method.

**Finally, if you are still not sure what to do about the pills you have missed:**

Use a back-up method (such as condoms and spermicides) anytime you have sex.

Contact your healthcare provider and continue taking one active pink pill each day until otherwise directed.

### **WHO SHOULD NOT TAKE Beyaz?**

Your healthcare provider will not give you Beyaz if you:

- Ever had blood clots in your legs (deep vein thrombosis), lungs (pulmonary embolism), or eyes (retinal thrombosis)
- Ever had a stroke
- Ever had a heart attack
- Have certain heart valve problems or heart rhythm abnormalities that can cause blood clots to form in the heart
- Have an inherited problem with your blood that makes it clot more than normal

- Have high blood pressure that medicine can't control
- Have diabetes with kidney, eye, nerve, or blood vessel damage
- Ever had certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision
- Ever had breast cancer or any cancer that is sensitive to female hormones
- Have liver disease, including liver tumors
- Have kidney disease
- Have adrenal disease

Also, do not take birth control pills if you:

- Smoke and are over 35 years old
- Are or suspect you are pregnant

Birth control pills may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy (also called cholestasis of pregnancy).

Tell your healthcare provider if you have ever had any of the above conditions (your healthcare provider can recommend another method of birth control).

Tell your healthcare provider if you are already taking daily folate supplements.

### **What Else Should I Know about Taking Beyaz?**

Birth control pills do not protect you against any sexually transmitted disease, including HIV, the virus that causes AIDS.

Do not skip any pills, even if you do not have sex often.

If you miss a period, you could be pregnant. However, some women miss periods or have light periods on birth control pills, even when they are not pregnant. Contact your healthcare provider for advice if you:

- Think you are pregnant
- Miss one period and have not taken your birth control pills every day
- Miss two periods in a row

Birth control pills should not be taken during pregnancy. However, birth control pills taken by accident during pregnancy are not known to cause birth defects.

You should stop Beyaz at least four weeks before you have major surgery and not restart it until at least two weeks after the surgery due to an increased risk of blood clots.

If you are breastfeeding, consider another birth control method until you are ready to stop breastfeeding. Birth control pills that contain estrogen, like Beyaz, may decrease the amount of milk you make. A small amount of the pill's hormones pass into breast milk.

If you are currently on daily, long-term treatment for a chronic condition with any of the following medications, you should consult your healthcare provider before taking Beyaz:

- NSAIDs (ibuprofen, naproxen and others)
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- ACE inhibitors (captopril, enalapril, lisinopril and others)

- Angiotensin-II receptor antagonists (Cozaar, Diovan, Avapro and others)
- Heparin
- Aldosterone antagonists

Tell your healthcare provider about all medicines and herbal products that you take. Some other medicines and herbal products may make birth control pills less effective, including:

- Barbiturates
- Bosentan
- Carbamazepine
- Felbamate
- Griseofulvin
- Oxcarbazepine
- Phenytoin
- Rifampin
- St. John's wort
- Topiramate

Consider using another birth control method when you take medicines that may make birth control pills less effective.

Birth control pills may interact with lamotrigine, an anticonvulsant used for epilepsy. This may increase the risk of seizures, so your healthcare provider may need to adjust the dose of lamotrigine.

Folates may make certain drugs, including some used for epilepsy, less effective, so talk to your healthcare provider about any medicines you take.

If you have vomiting or diarrhea, your birth control pills may not work as well. Use another birth control method, like condoms and a spermicide, until you check with your healthcare provider.

If you are scheduled for any laboratory tests, tell your doctor you are taking birth-control pills. Certain blood tests may be affected by birth-control pills.

### **What are the Most Serious Risks of Taking Birth Control Pills?**

Like pregnancy, birth control pills increase the risk of serious blood clots, especially in women who have other risk factors, such as smoking, obesity, or age greater than 35. It is possible to die from a problem caused by a blood clot, such as a heart attack or a stroke. Some examples of serious clots are blood clots in the:

- Legs (thrombophlebitis)
- Lungs (pulmonary embolus)
- Eyes (loss of eyesight)
- Heart (heart attack)
- Brain (stroke)

A few women who take birth control pills may get:

- High blood pressure

- Gallbladder problems
- Rare cancerous or noncancerous liver tumors

All of these events are uncommon in healthy women.

**Call your healthcare provider right away if you have:**

- Persistent leg pain
- Sudden shortness of breath
- Sudden blindness, partial or complete
- Severe pain in your chest
- Sudden, severe headache unlike your usual headaches
- Weakness or numbness in an arm or leg, or trouble speaking
- Yellowing of the skin or eyeballs

**What are the Common Side Effects of Birth Control Pills?**

The most common side effects of birth control pills are:

- Spotting or bleeding between menstrual periods
- Nausea
- Breast tenderness
- Headache

These side effects are usually mild and usually disappear with time.

Less common side effects are:

- Acne
- Less sexual desire
- Bloating or fluid retention
- Blotchy darkening of the skin, especially on the face
- High blood sugar, especially in women who already have diabetes
- High fat (cholesterol; triglyceride) levels in the blood
- Depression, especially if you have had depression in the past. Call your healthcare provider immediately if you have any thoughts of harming yourself.
- Problems tolerating contact lenses
- Weight changes

This is not a complete list of possible side effects. Talk to your healthcare provider if you develop any side effects that concern you. You may report side effects to the FDA at 1-800-FDA-1088.

No serious problems have been reported from a birth control pill overdose, even when accidentally taken by children.

### **Do Birth Control Pills Cause Cancer?**

Birth control pills do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use birth control pills because some breast cancers are sensitive to hormones.

Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

### **What Should I Know about My Period when Taking Beyaz?**

Irregular vaginal bleeding or spotting may occur while you are taking Beyaz. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding, which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle, is unusually heavy, or lasts for more than a few days, call your healthcare provider.

Some women may not have a menstrual period but this should not be cause for alarm as long as you have taken the pills according to direction.

### **What if I Miss My Scheduled Period when Taking Beyaz?**

It is not uncommon to miss your period. However, if you miss two periods in a row or miss one period when you have not taken your birth control pills according to directions, call your healthcare provider. Also notify your healthcare provider if you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. It is important that your healthcare provider checks you to find out if you are pregnant. Stop taking Beyaz if you are pregnant.

### **What If I Want to Become Pregnant?**

You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill. See your health care provider about appropriate folate supplementation if you stop taking Beyaz, are pregnant, or plan on becoming pregnant.

### **General Advice about Beyaz**

Your healthcare provider prescribed Beyaz for you. Please do not share Beyaz with anyone else. Keep Beyaz out of the reach of children.

If you have concerns or questions, ask your healthcare provider. You may also ask your healthcare provider for a more detailed label written for medical professionals.

Bayer HealthCare Pharmaceuticals Inc.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

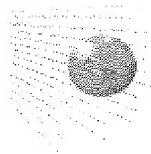
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/s/

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JULIE G BEITZ

09/24/2010



"Lucarelli, Pamela K"  
<Pamela.Lucarelli@fda.hhs.gov>

09/24/2010 04:45 PM

To "Kavita Johal" <kavita.johal@bayer.com>

cc

bcc

Subject NDA 022532 Approval Letter

Kavita,

Attached is the letter. If you have any questions, please let me know.

Pam

Pamela Lucarelli  
Regulatory Health Project Manager  
FDA/Center for Drug Evaluation and Research  
Division of Reproductive and Urologic Products  
WO22 - Room 5323  
10903 New Hampshire Avenue  
Silver Spring, MD 20903

Phone 301.796.3961  
Fax 301.796.9897  
pamela.lucarelli@fda.hhs.gov



NDA 022532 Approval Letter FINAL.pdf

**EXHIBIT B**